

IN THE CLAIMS

Claims 1 and 6 have been amended to recite "wherein the DNA, other than for any substitution of the G residue at position 434, comprises a nucleotide sequence identical to the sequence of residues 432-435 of SEQ ID NO: 1." Support for this subject matter is found in the specification, for instance, in the paragraph bridging pp. 22 and 23, and in Figure 2 in which the ACGT residues at positions 432-435 are indicated in bold to indicate the polymorphic splice site (see also the description of Fig. 2 at p. 5).

For the sake of brevity, Claim 1 has also been amended to recite "wherein the substitution of the G residue with an A residue at position 434 causes the splicing defect." Support for this subject matter is found in the previous version of the claim.

Claims 3 and 8 have been amended to delete the recital of "complementary to a subregion of the human dihydropyrimidine dehydrogenase genomic nucleotide sequence of SEQ ID NO: 1" and to recite in place thereof "from about 15 to about 20 nucleotides long and wherein the nucleotides are in a sequence complementary to a sequence of SEQ ID NO: 1 located between position 434 and 861." Support for the length of the primers is found in the specification in the second full paragraph on p. 15. Support for the recital of from position 434 to 861 is found, *inter alia*, in original claim 3 which recited complementarity to an *intronic* sequence (e.g., sequences 434-861). The use of such primers is exemplified in the specification at p. 15, last full paragraph, (e.g., DELR1) and further described in the three full paragraphs of page 15.

The recital "PCR" in claims 3, 8, and 10 has been replaced by the phrase "polymerase chain reaction." Support for this substitution is found in the specification at p. 14, line 20.

Claims 4 and 9 have been amended to recite "Mae II restriction endonuclease." Support for this subject matter is found in the specification in the paragraph bridging pp. 22 and 23.

Claim 6 has been amended to recite "wherein the DNA comprises positions 432-435 of SEQ ID NO: 1." Support for the claimed subject matter is found, for instance, in the specification in the description of Figure 1 at p. 5; and in the section beginning on p. 11 titled "PCR Amplification of the Intron-Exon Boundaries of the DPD Gene." Support for this subject matter is also found in the paragraph bridging pp. 22 and 23, and in Figure 2 in which the ACGT residues at positions 432-435 are indicated in bold to indicate the polymorphic slice site (see also the description of Fig. 2 at p. 5).

Claim 10 was amended to recite "from about 15 to about 20 nucleotides long wherein the nucleotide sequence is complementary to a nucleotide sequence of SEQ ID NO: 1 located between position 434 and position 861." Support for the length of the primers is found in the specification in the second full paragraph on p. 15. Support for the recital of from position 434 to 861 is found in the previous claim which recited an *intronic* sequence and in Figure 1, for instance, which indicated the intronic sequence from position 434-861. The use of such primers is exemplified in the specification at p. 15, last full paragraph, (e.g., DELR1) which recites an "adjacent introns" as suitable targets for primers. The recited intronic sequence is such.

Claim 11 was amended to recite "wherein the nucleotides are in a sequence corresponding to a sequence of SEQ ID NO: 1 located between position 434 and position 534." This amendment finds support in previous claim 11 which also depended from claim 10. Previous claim 11 provided a primer complementary to a subregion of a human dihydropyrimidine dehydrogenase intronic genomic nucleotide sequence located within 100 nucleotides of the position indicated as nucleotide 434 of SEQ ID NO: 1.

In view of the above, Applicants believe the amendments to the claims add no new matter and respectfully request their entry.

Response to Rejection of Claims 1-5, 8, 10, 11, 15, 20, 22, 24 and 26 under 35 U.S.C. §112, 2nd Paragraph.

A. Recital of "said gene" in Claim 1.

The Action alleged Claim 1 (and claims 2-5 dependent therefrom) to be confusing in reciting "wherein said gene the substitution of the G residue with an A residue at said position." The Examiner indicated he interpreted the term to mean "wherein the substitution of the G residue with an A residue at said position." Applicants have amended the claim to recite the Examiner's interpretation.

In light of the above, Applicants request that this grounds for rejection be reconsidered and withdrawn.

B. Recital of "Subregion ... of SEQ ID NO:1" in claims 3, 8, 10, 11, 15, 20, 22, 24, and 26.

The Action alleged the various recitals of "subregion" in claims 3, 8, 10, 11, 15, 20, 22, 24, and 26 were not clear and suggested that the Applicants recite the specific nucleotides that are encompassed within the scope of the claims. As noted above, Applicants have cancelled claims 15, 20, 22, 24, and 26; and have amended claims 3, 8, 10, and 11 as discussed below.

Claims 3, 8, 10, 11

Without acquiescing to the position of the Action, Applicants have amended claims 3, 8, 10, and 11 to delete the recital at issue. Claims 3 and 8 now recite instead primers "from about 15 to 20 nucleotides long and wherein the nucleotides are in a sequence complementary to a sequence of SEQ ID NO. 1 located between position 434 and 861." Applicants are limited by the Support in the specification, but believe these proposed amendments substantially accomplish the same objectives sought by the Examiner.

Claim 10, as amended, has a similar recital. Claim 11 depends from claim 10, and recites "a sequence of SEQ ID NO: 1 located between position 434 and position 534."

Applicants submit that the metes and bounds of these claims, as amended, are well defined and easily understood by one of ordinary skill. The nucleotide sequences of the complementary antisense and sense strands are both actually set forth in Figure 1. Furthermore, Figure 1 illustrates with DELR1 how such a primer can be readily identified. For instance, a primer falls within the scope of the primers of the claims merely by being about 15 -20 nucleotides long and having the sequence of a similar length of a strand complementary to the targeted portion of SEQ ID NO: 1. Complementary, antisense strand sequences are laid out in Figure 1.

In light of the above, Applicants request that the above rejections be reconsidered and withdrawn.

Response to the Rejection of Claims 1-4, 8-10, 15-17, 20, 22 24, 26, and 27 under 35 U.S.C. §112, first Paragraph.

Written Description of the Human DPD Genome recited in Claims 1 and 6.

As discussed with the Examiner on November 14, 2002, with respect to the written description of the DPD genomic subject matter, Applicants have amended each of the base methods claims (Claims 1 and 6). The amended base claims now also recite the sequence of the particular splicing junction about the discovered polymorphism at position 434 of SEQ ID NO: 1.

As a threshold matter, it is important to establish what the claims recite and do not recite. These *methods* claims are directed in part to detecting a DPD genomic DNA mutation in a specified sequence of one particular splicing junction of the gene. Claim 1, in particular, recites:

A method of detecting a splicing defect in a human dihydropyrimidine dehydrogenase gene, comprising determining whether the residue of a human genomic DNA encoding the human dihydropyrimidine dehydrogenase gene at the position indicated as nucleotide 434 of SEQ ID NO:

1 is a G residue or determining whether the residue at the position indicated as nucleotide 434 of SEQ ID NO: 1 is an A residue, wherein the substitution of the G residue with an A residue at position 434 causes the splicing defect in the human dihydropyrimidine dehydrogenase gene; and wherein the DNA, other than for any substitution of the G residue at position 434, comprises a nucleotide sequence identical to the sequence of residues 432-435 of SEQ ID NO: 1.

Claim 6, in particular, recites:

A method of screening human patients for sensitivity to 5-fluorouracil, comprising isolating a genomic DNA from the patient, wherein the DNA comprises positions 432-435 of SEQ ID NO: 1; and determining whether a G residue is the nucleotide at position 434, and wherein the DNA, other than for any substitution of the G residue at position 434, comprises a nucleotide sequence identical to the sequence of residues 432-435 of SEQ ID NO: 1.

The Action alleges that the Applicants have taught only one species of the genus of the DPD genomic DNA. However, the Applicants do not claim the genus of DPD genomic DNA. They claim methods operating upon the genus. The specification demonstrates the method operates upon the genus and therefore fully satisfies the written description requirement. See Table II at p. 28, which tested over 150 subjects of diverse ethnic backgrounds (Japanese, African American, Finnish, Taiwanese, and British populations.). To the extent that a method of detecting the mutation in the allegedly heterogeneous DPD genomic DNA is the issue, the Applicants have therefore applied the method to populations which are sufficiently large and diverse in origins so as to have captured any of the alleged heterogeneity posited by the Examiner. Thus, assuming for the sake of argument, that one of ordinary skill in the art would have expected substantial DPD heterogeneity at the time of invention, the Applicants have described the use of their method on that same genus. Here, the Applicants are only claiming subject matter they well exemplified and well described.

While the application goes much further than to disclose a method operating upon a single species of DPD genomic DNA, according to MPEP § 2163, even a single species can be sufficient to claim a genus as a whole:

A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. On the other hand, there may be situations where one species adequately supports a genus. (Emphasis added)

Even assuming for the sake of argument that the Applicants had not tested over a 150 ethnically diverse members of the human community, the subject matter of the claims would clearly fall within the precedent cited by the MPEP § 2163:

In re Herschler, 591 F.2d 693, 697, 200 USPQ 711, 714 (CCPA 1979) (disclosure of corticosteroid in DMSO sufficient to support claims drawn to a method of using a mixture of a "physiologically active steroid" and DMSO because "use of known chemical compounds in a manner auxiliary to the invention must have a corresponding written description only so specific as to lead one having ordinary skill in the art to that class of compounds. Occasionally, a functional recitation of those known compounds in the specification may be sufficient as that description."). See Eighth edition of MPEP § 2163 at p.2100-170, middle of the right column).

Here, the Applicants taught 1) the point mutation they discovered to be the cause of the splicing defect; 2) the existence of the mutation in more than one human pedigree (see Examples 1 and 2) having the enzyme deficiency; and 3) the mutation causes a potentially fatal susceptibility to a commonly prescribed cancer medication. Without more, the specification would motivate one of ordinary skill in the art to perform the claimed method on cancer patient populations to be administered 5-fluorouracil to see if they were at risk of the drug reaction. This patient population would not be selected according to their DPD genomic status but according to their disease status and so would inherently represent a sampling of the human DPD genomic DNA diversity. As with *In Re Herschler*, the functional description of the Applicants methods would lead one of ordinary skill to testing the compounds on the genus of DPD genomic DNA.

In view of the above, the Applicants respectfully request that the above rejection be reconsidered and withdrawn.

Primer Subject Matter (Primers are recited in claims 3, 8, 10, 11, 15, 20, 22 and 24).

Without acquiescing to the position of the Action, claims 15, 20, 22 and 24 have been canceled to expedite prosecution of the application. Because claims 3 and 8 involve issues in addition to those of claims 10 and 11, claims 10 and 11 will be addressed first.

Claims 10 and 11.

Claim 10 has been amended to recite:

A composition comprising a polymerase chain reaction primer from about 15 to about 20 nucleotides long wherein the nucleotide sequence is complementary to a nucleotide sequence of SEQ ID NO: 1 located between position 434 and position 861.

Claim 11 depends from claim 10 and is drawn to primers having a nucleotide sequence complementary to a nucleotide sequence located between positions 434 and 534. The subject matter thereof is exemplified by the primer DELR1 (see Figure 1).

In accordance with the precedent of *In Re Herschler*, one of ordinary skill in the art would directly be lead to select and use other primers complementary to this portion of the DPD genomic DNA. The specification expressly teaches the use of such primers (see last two full paragraphs on p. 15, for instance) and actually spells out the antisense and sense sequences for this portion of the DNA genomic sequence. This figure underlines the DELR1 sequence. A variety of other 15-20 nucleotide long primer sequences would be readily apparent to one of ordinary skill in the art, merely by similarly applying ruler and pencil to other stretches of the genomic DNA between positions 434 and 861. Nothing could be more direct or simpler.

Claims 3 and 8

Claims 3 and 8, as amended, are drawn to in part to the use of primers complementary to a sequence of SEQ ID NO: 1 from position 434 to 861 in detecting a mutation of DPD genomic DNA at the particular position denoted by nucleotide 434 of

SEQ ID NO: 1. Thus, the polymorphism of DPD genomic DNA remains relevant as to the written description requirement for the subject matter of these particular claims.

With respect to these claims, in addition to the above discussion concerning the written description of methods operating upon the genus of DPD genomic DNA, Applicants would like to point out that the Examiner has acknowledged that

"one of ordinary skill in the art at the time the invention would have been able to use primers designed based on the human cDNA sequence, which was known at the time of the invention, to sequence between exons using human genomic DNA in order to determine the intronic sequences of human DPD genomic DNA."

The Examiner thus posits that, at the time the invention was made, one of ordinary skill would have been lead to selecting primers from the *exonic* sequences of the DPD genomic DNA for the purposes of determining the DPD genomic sequence without regard to the alleged substantial variation of the DPD genomic sequence or knowledge of the particular mutation site. Certainly, if the variation of genomic DNA was no barrier to selection and use of primers complementary to *exonic* genomic DNA by one of ordinary skill, it would have been no barrier to the similar selection and similar use of primers complementary to the discovered *intronic* genomic DNA by one of ordinary skill.

Applicants submit that one of ordinary skill would also have been much more readily lead to the use of the recited *intronic* sequences to identify and determine the residue of a *known* mutation site of the same genomic DNA as that is precisely what is taught (see p. 15, last two paragraphs) and exemplified (e.g., DELR1) by the specification. What was true of the *exonic* genomic DNA should be even more true of the *intronic* genomic DNA.

In view of the above, Applicants request that the above rejections be reconsidered and withdrawn.

Response to Rejection of Claims 4, 9, 17, and 27 stand rejected under 35 U.S.C. §112, first paragraph for an alleged lack of enablement.

The Action rejected the claims as not enabled in the scope claimed with respect to the restriction endonuclease subject matter. In order to expedite prosecution of the application, and without acquiescing to the position of the Action, claims 17 and 27 have been canceled and claims 4 and 9 have been amended to recite the Mae II restriction endonuclease exemplified in the specification.

Applicants therefore respectfully request that the above grounds for rejection be reconsidered and withdrawn.

Response to Rejection of Claims 10, 11, 15, and 24 under 35 U.S.C. §103(a) as being unpatentable over Gonzalez et al. in view of Meinsma et al.

In order to expedite prosecution of the application, and without acquiescing to the positions of the Examiner, applicants have canceled claims 15 and 24 and amended claims 10 and 11.

Each of the claims as amended are now drawn, at least in part, to a primer about 15 to 20 residues in length which are complementary to a polynucleotide having a sequence of SEQ ID NO: 1 from position 434 to 861 (Claim 10) and or from position 434 to 534 (Claim 11).

The polynucleotide sequence of SEQ ID NO: 1 from 434 to 534 or 434 to 861 is not found in either Meinsma et al. or Gonzalez et al. Even if the references do provide a motivation to determine the sequence of this intronic region, the motivation does not render the sequence obvious. MPEP §2141.09 (2100-148, bottom left column) and the courts require more. See *In re Deuel*, 51 F.3d 1552 at 1559, 34 U.S.P.Q.2d 1210 at 1215 (Fed. Cir. 1995) (“**A general motivation to search for some gene that exists does not necessarily make obvious a specifically-defined gene that is subsequently obtained as a result of that search.**” (emphasis added)).

Moreover, the cited reference of Gonzalez et al. et al, Trends in Pharmaceutical Sciences 16(10):325-327 (1995) **is not prior art**<sup>1</sup> under 35 U.S.C. §102(a) or (b). With respect to 35 U.S.C. §102(a), the authors of the Gonzalez et al. reference (Drs. Gonzalez and Fernandez-Salguero) are the same persons who are the inventors of the instant application. Thus, this reference does not show prior invention by another. With respect to 35 U.S.C. §102(b), the cited reference has a publication date of October 1995. The present application has the earliest priority date of March 20, 1996. Thus, as the cited reference was published within one year of the priority date, the reference is not available as prior art under 35 U.S.C. §102(b).

In view of the above, Applicants request that the above rejections be reconsidered and withdrawn.

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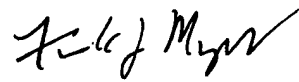
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<sup>1</sup> As evidence thereof, Applicants cite the publication date of October, 1995 (see enclosed title page of the journal) which is only 6 months prior to the earliest priority date. Unfortunately, this title page was not stamped with the date it was received by the library, so we also copied the September 1995 and November 1995 issues of the publication which were stamped with their receipt dates of September 22, 1995 and November 20, 2002.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is urged. If the Examiner believes a telephone conference would aid in the prosecution of this case in any way, please call the undersigned at 925-472-5000.

Respectfully submitted,



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**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

**In the claims:**

Claims 15-17 and 20-28 have been cancelled without prejudice.

Claims 1, 3, 4, 6, and 8-11 have been amended to read as follows:

1. (Three times amended) A method of detecting a splicing defect in a human dihydropyrimidine dehydrogenase gene, comprising determining whether the residue of a human genomic DNA encoding the human dihydropyrimidine dehydrogenase gene at the position indicated as nucleotide 434 of SEQ ID NO: 1 is a G residue or determining whether the residue at the position indicated as nucleotide 434 of SEQ ID NO: 1 is an A residue, wherein [said gene] the substitution of the G residue with an A residue at [said position] position 434 causes [a] the splicing defect in the human dihydropyrimidine dehydrogenase gene; and wherein the DNA, other than for any substitution of the G residue at position 434, comprises a nucleotide sequence identical to the sequence of residues 432-435 of SEQ ID NO: 1.

3. (Three times amended) The method of claim 2, wherein the method comprises amplifying the genomic DNA with a polymerase chain reaction primer from about 15 to about 20 nucleotides long and wherein the nucleotides are in a sequence complementary to a sequence of SEQ ID NO: 1 located between position 434 and 861. [complementary to a subregion of the human dihydropyrimidine dehydrogenase genomic nucleotide sequence of SEQ ID NO: 1.]

4. (Three times amended) The method of claim 2, wherein the detecting is by digestion of the amplified DNA with a Mae II restriction endonuclease.

6. (Three times amended) A method of screening human patients for sensitivity to 5-fluorouracil, comprising isolating a genomic DNA from the patient, wherein the DNA comprises positions 432-435 of SEQ ID NO: 1; and determining whether a G residue is the nucleotide at position 434, and wherein the DNA, other than for any substitution of the G residue at position 434, comprises a nucleotide sequence

identical to the sequence of residues 432-435 of SEQ ID NO: 1. [residue of the DNA at the position indicated as nucleotide 434 of SEQ ID NO: 1.]

8. (Three times amended) The method of claim 7, wherein the method comprises amplifying the genomic DNA with a polymerase chain reaction primer from about 15 to about 20 nucleotides long and wherein the nucleotides are in a sequence complementary to a sequence of SEQ ID NO: 1 located between position 434 and 861. [complementary to a subregion of the human dihydropyrimidine dehydrogenase genomic nucleotide sequence of SEQ ID NO: 1.]

9. (Three times amended) The method of claim 7, wherein the determining is by digestion of the amplified DNA with a Mae II restriction endonuclease.

10. (Three times amended) A composition comprising a [PCR] polymerase chain reaction primer from about 15 to about 20 nucleotides long wherein the nucleotide sequence is complementary to a nucleotide sequence of SEQ ID NO: 1 located between position 434 and position 861. [complementary to a subregion of a human dihydropyrimidine dehydrogenase intronic genomic nucleotide sequence of SEQ ID NO: 1.]

11. (Three times amended) The composition of claim 10, wherein the nucleotides are in a sequence corresponding to a sequence of SEQ ID NO: 1 located between position 434 and position 534. [PCR primer is complementary to a subregion of a human dihydropyrimidine dehydrogenase intronic genomic nucleotide sequence located within 100 nucleotides of the position indicated as nucleotide 434 of SEQ ID NO: 1.]

## **APPENDIX I**

### **COMPLETE SET OF PENDING CLAIMS**

1. (Three times amended) A method of detecting a splicing defect in a human dihydropyrimidine dehydrogenase gene, comprising determining whether the residue of a human genomic DNA encoding the human dihydropyrimidine dehydrogenase gene at the position indicated as nucleotide 434 of SEQ ID NO: 1 is a G residue or determining whether the residue at the position indicated as nucleotide 434 of SEQ ID NO: 1 is an A residue, wherein the substitution of the G residue with an A residue at position 434 causes the splicing defect in the human dihydropyrimidine dehydrogenase gene; and wherein the DNA, other than for any substitution of the G residue at position 434, comprises a nucleotide sequence identical to the sequence of residues 432-435 of SEQ ID NO: 1.
2. (Twice amended) The method of claim 1, wherein the method comprises the step of amplifying human intronic dihydropyrimidine dehydrogenase genomic DNA to detect therein a G residue or an A residue at the position indicated as nucleotide 434 of SEQ ID NO: 1.
3. (Three times amended) The method of claim 2, wherein the method comprises amplifying the genomic DNA with a polymerase chain reaction primer from about 15 to about 20 nucleotides long and wherein the nucleotides are in a sequence complementary to a sequence of SEQ ID NO: 1 located between position 434 and 861.
4. (Three times amended) The method of claim 2, wherein the detecting is by digestion of the amplified DNA with a Mae II restriction endonuclease.
5. (Twice amended) The method of claim 1, wherein the determining is by oligonucleotide array.

6. (Three times amended) A method of screening human patients for sensitivity to 5-fluorouracil, comprising isolating a genomic DNA from the patient, wherein the DNA comprises positions 432-435 of SEQ ID NO: 1; and determining whether a G residue is the nucleotide at position 434, and wherein the DNA, other than for any substitution of the G residue at position 434, comprises a nucleotide sequence identical to the sequence of residues 432-435 of SEQ ID NO: 1.

7. (Twice amended) The method of claim 6, wherein the method comprises the step of amplifying human intronic dihydropyrimidine dehydrogenase genomic DNA from the patient and determining if the residue at the position indicated as nucleotide 434 of SEQ ID NO: 1 is a G residue or determining if the residue at the position indicated as nucleotide 434 of SEQ ID NO: 1 is an A residue.

8. (Three times amended) The method of claim 7, wherein the method comprises amplifying the genomic DNA with a polymerase chain reaction primer from about 15 to about 20 nucleotides long and wherein the nucleotides are in a sequence complementary to a sequence of SEQ ID NO: 1 located between position 434 and 861.

9. (Three times amended) The method of claim 7, wherein the determining is by digestion of the amplified DNA with a Mae II restriction endonuclease.

10. (Three times amended) A composition comprising a polymerase chain reaction primer from about 15 to about 20 nucleotides long wherein the nucleotide sequence is complementary to a nucleotide sequence of SEQ ID NO: 1 located between position 434 and position 861.

11. (Three times amended) The composition of claim 10, wherein the nucleotides are in a sequence corresponding to a sequence of SEQ ID NO: 1 located between position 434 and position 534.